Systemic sclerosis: can we identify patients at risk?

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Chapter 7

Degree of vasculopathy in systemic sclerosis patients with anti-U3RNP antibody indicates need for extensive cardiopulmonary screening

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TO THE EDITOR:

In patients with systemic sclerosis (SSc) regular screening is needed to determine the extent and severity of organ involvement(1). Specific autoantibodies are associated with clinical manifestations and are therefore used as predictors for organ involvement(2). Identifying patients who are at risk for organ involvement enables distinguishing between patients with high risk that need extensive screening and follow-up, and patients with most likely mild disease. Antibodies against the U3-ribonucleoprotein (U3RNP or anti-fibrillarin) are detected in 3-8% of SSc patients. Some studies indicate a higher risk for cardiac involvement in U3RNP+ patients, but results are conflicting(3-7). As shown before, the degree of microangiopathy as reflected by nailfold videocapillaroscopy (NVC) is identified as independent predictor for organ involvement in SSc(8). Associations between presence of U3RNP and NVC pattern and disease manifestations have however, not been evaluated thus far. Therefore, we evaluated degree of microangiopathy as shown by NVC and its association with cardiopulmonary involvement in anti-U3RNP + SSc patients.

All patients participating in the Combined Care in Systemic Sclerosis (CCISS) prospective observational cohort study (approved by the Ethics Committee P09.003/SH/sh) of the Leiden University Medical Center gave written informed consent. Eighteen U3RNP+ patients (indicating a prevalence of 3% in the CCISS cohort) were compared with an equal number of age- and sex matched anticentromere+ (ACA) and antitopoisomerase+ (ATA) controls. Although controls were not matched for disease duration, there were no significant differences between the groups. Cardiopulmonary screening was performed routinely in all patients.

Myocardial involvement was defined using a combined value where patients had to have at least two of the following: arrhythmias (>2% ventricular/supraventricular arrhythmia or atrial fibrillation), conduction problems (atrioventricular/bundle branch blocks), left ventricular ejection fraction (LVEF)< 50%, diastolic dysfunction, or pericardial effusion. Pulmonary involvement was defined based on the combination of diffusion capacity for carbon monoxide (DLCO)<60% and forced vital capacity (FVC)<70% and evidence for interstitial lung disease (ILD) on high resolution computed tomography (HRCT). NVC was performed at baseline, and images were classified by a trained observer as early, active or late SSc pattern (9). In addition capillary loss (<7 per mm) was determined.

U3RNP+ patients were most often female (78%), with a high prevalence of diffuse cutaneous SSc (dcSSc 39%) and 22% was of African-American origin (n= 4); compared to 0% among the ACA and ATA+ patients. This confirms the results of other studies in which an association between U3RNP antibody, skin score and African-American race

was found. Myocardial involvement was present in 17% (n= 3) of the U3RNP+ patients compared to 17% (n= 3) in the ACA+ and 33%(n= 6) in the ATA+ patients. Pulmonary involvement was present in 6% (n= 1) of the U3RNP+ patients compared to 6% (n= 1) in the ACA+ and 29% (n= 5) in the ATA+ patients. Based on these data we cannot confirm a higher prevalence of cardiopulmonary involvement in patients with U3RNP antibody compared with ACA+/ATA+ patients. As mean skin scores and pulmonary function test results were clearly worse in U3RNP+ patient as compared to ACA patients, indicating more severe disease with possible higher risk, we consequently evaluated whether degree of microangiopathy could add to distinguish those U3RNP patients at risk for cardiopulmonary involvement. The distribution of SSc patterns among U3RNP+ and ATA+ patients was comparable; in the ACA+ patients a late SSc pattern and capillary loss were less common (figure 1).

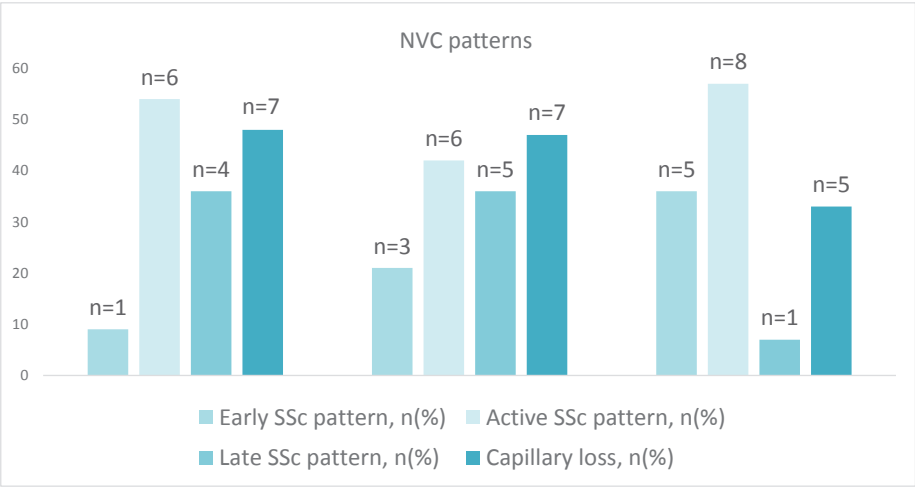

Figure 1. Distribution of nailfold videocapillaroscopy patterns among the autoantibodies. SSc= Systemic Sclerosis. U3RNP= U3-ribonucleoprotein positive patients, ATA= antitopoisomerase positive patients, ACA= anticentromere positive patients. In the U3RNP group 3 patients had secondary pattern and 1 an aspecific pattern, in the ACA and ATA group only 1 patient had a secondary pattern.

For the complete population, with NVC available (n= 45), late NVC pattern was associated with pulmonary involvement (X^2, p= 0.03; table 1) and capillary loss with myocardial involvement (X^2, p= 0.05; table 1). Nevertheless, we do believe that it is the severity of microangiopathy that is associated with both cardiac and pulmonary involvement and do not consider late pattern and capillary loss as different pathophysiological processes . When selecting all U3RNP+ patients (n= 18) for extensive cardiopulmonary screening, cardiopulmonary involvement was detected in 11% (2 out of 18). When only selecting U3RNP+ patients with either late SSc pattern or capillary loss, extensive screening was necessary in 47% of U3RNP+ patients (7 out of 15 patients), and none of the U3RNP+ patients with cardiopulmonary involvement was missed.

Total group and U3RNP+ group, SSc pattern, capillary loss and organ involvement

	Cardiac involvement -	**Cardiac involvement +**	**Pulmonary involvemement -**	**Pulmonary involvement +**
All	n=37	n=8	n=42	n=3
Early, n=9	8 (22%)	1 (13%)	9 (21%)	0 (0%)
Active, n=20	18 (47%)	2 (26%)	20 (58%)	0 (0%)
Late, n=10	6 (17%)	4 (52%)	7 (17%)	**3 (100%)***
Secundary, n=6	5 (14%)	1 (13%)	6 (14%)	0 (0%)
U3RNP+	n=13	n=2	n=15	n=0
Early, n=1	1 (8%)	0 (0%)	1 (6%)	0 (0%)
Active, n=6	6 (46%)	0 (0%)	6 (40%)	0 (0%)
Late, n=4	3 (23%)	1 (50%)	4 (27%)	0 (0%)
Secundary, n=4	3 (23%)	1 (50%)	4 (27%)	0 (0%)
All	n=37	n=8	n=42	n=3
Capillary loss -, n=26	24 (65%)	2 (25%)	26 (62%)	0 (0%)
Capillary loss +, n=19	13 (35%)	**6 (75%)****	16 (38%)	3 (100%)
U3RNP+	n=13	n=2	n=15	n=0
Capillary loss -, n=8	8 (61%)	0 (0%)	8 (53%)	0 (0%)
Capillary loss +, n=7	5 (39%)	2 (100%)	7 (47%)	0 (0%)

Table 1. *Total group and U3RNP+ group, SSc pattern, capillary loss and organ involvement.* * p= 0.009 chi square; late pattern vs non late pattern, ** = p value 0.047 chi square; capillary loss vs no loss, all other comparisons non-significant.Cardiac involvement defined as a Medsger score of 1 or higher, or at least two of the following: decreased LVEF, arrhythmias, conduction abnormalities, diastolic dysfunction or pericardial effusion, pulmonary involvement defined as decreased FVC and DLCO and ILD on HRCT

To our knowledge, this is the first study to describe NVC findings in U3RNP+ SSc patients, and associate NVC patterns with cardiopulmonary involvement in this group. The strength of the presented data lies in the prospective study design with standardized annual follow-up independent of clinical presentation. However, given the low numbers, our findings need replication. As previously shown, U3RNP antibody was more prevalent among African-Americans. We could not confirm previous suggestions of a higher prevalence of cardiac involvement in this group. Our data confirm that in SSc the degree of microangiopathy as reflected by NVC is associated with severity of cardiopulmonary involvement, this is also true in U3RNP+ patients. As such, NVC can serve as biomarker to select U3RNP+ SSc patients with higher risk for cardiopulmonary involvement.

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